

REMARKS

Claims 34 and 36 have been amended. That amendment is supported by the application as originally filed. The Examiner is thanked for the courtesy of the telephone interview of November 6, 2003.

In Paper No. 23, the Examiner repeated the rejection of claims 1 to 13 and 15 to 34 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,132,771 to Depui et al. ("Depui"). Additionally, claims 1 to 13 and 15 to 40 were rejected under 35 U.S.C. §103(a) as unpatentable over Depui. Further, claims 1 and 35 were rejected for obviousness based on the combination of Depui in view of European Patent Specification 244 380 B1 to Lovgren et al. It is believed that U.S. Patent No. 4,853,230 is the U.S. counterpart to that European specification. It is submitted these rejections are improper and should be withdrawn.

For a reference to anticipate a claimed invention, that single reference must show each and every feature of the claimed invention arranged as in the claim. See *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193 (Fed. Cir. 1993). That reference must contain sufficient disclosure as to convince one of ordinary skill in the art that the inventor had possession of the invention at the time the reference was filed. When a composition is claimed, an anticipating reference must completely identify the claimed composition, as it is set forth in the claim, and must also provide an enabling disclosure so that one of ordinary skill in the art can, without undue experimentation, make the invention. See *In re Sheppard* 144 U.S.P.Q. 42 (CCPA 1964). If a reference fails to properly identify the invention or to enable one to make the invention without undue experimentation, that reference does not describe the invention and cannot be an anticipatory reference.

It is submitted that the Depui reference does not anticipate the now claimed invention. It neither identifies the claimed invention, nor does it enable one of ordinary skill in the art to make the invention without undue experimentation.

The Depui patent, assigned to Astra-Zeneca, is directed to an oral pharmaceutical dosage form for a combined therapy against GORD (Gastro Oesophageal Reflux Disease). The dosage form is preferably a tablet containing an acid suppressing agent (proton pump inhibitors i.e. omeprazol, lansoprazol,...) and a prokinetic agent (i.e. cisapride, mosapride,...).

The main objective of Depui is to provide an oral dosage form simultaneously containing both an acid suppressive agent and a prokinetic agent, but not enteric coating layered preparations of proton pump inhibitors.

In column 2, starting at line 47, Depui describes as obvious that the proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer and specifically refers to U.S. Patent

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No. 4,786,505 ("the '505 patent") for omeprazole preparations (see col. 2, lines 50-57) with a description of enteric coating layered preparations of proton pump inhibitors.

The '505 patent discloses omeprazole pellets having a core containing omeprazole and an alkaline substance, one or more separating layers, and an outer enteric coating. The separating layer(s) are described as necessary because: *"The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discoloration of omeprazole during the coating process or during storage."*(see '505 col. 3, lines 4-8). U.S. Patent No. 4,853,230 (the '230 patent), contains similar disclosure relating to other proton pump inhibitors (see col. 8, line 67 to col. 9, line 4).

Both the '505 (col. 3, lines 36 to 65) and the '230 (col. 8, lines 31 to 61) patents refer to the importance of the presence of an alkaline substance and both contain extensive disclosure as to the necessity of the separating layer because of the acid sensitivity of omeprazole and the negative experiences in bio-studies of compositions without the separating layer. The '505 patent refers to an article "Development of an Oral Formulation of Omeprazole", Scand. J. Gastroenterology, 1985, pgs. 113-120 describing conventional enteric coated dosage forms and their stabilization.

Depui fails to describe how a stable and useful oral form of a proton pump inhibitor can be made without having an alkaline reacting substance and at least one separating layer. That is to say, assuming that Depui contained sufficient disclosure to identify such a composition, it fails to contain enabling disclosure as to how to make such a composition. Further, it never discloses or suggests that the active layer is substantially non-porous. See line 3 of pending claim 1. Importantly, the rejection does not state, or suggest, that the reference shows or suggests this feature of the now claimed invention.

All 14 examples described by Depui refer to a proton pump inhibitor dosage form having an alkaline substance and at least one separating layer between the core and the surrounding enteric coating. The alkaline substance can be included as a basic salt of the corresponding proton pump inhibitor, i.e. omeprazole magnesium salt, as stated in the '505 (col. 4, lines 23 to 27) and '230 (col. 8, lines 55 to 61) patents. The references examples merely refer to the active layer being applied to the seed in a fluidized bed apparatus. There is not a single example, suggestion, description or mention of how to produce a stable and useful composition or composition with a substantially non-porous active layer as defined in the presently pending claims.

The Examiner in the Office Action, has referred to text regarding the enteric coating layer of proton pump inhibitors as "optional" for both the presence of alkaline reacting substances and separating layers(s).

However, that "optional" feature is referred to generally and it is not supported by the cited prior art or by the patent description. Since the main object of Depui is a combined therapy for GORD, Depui sought broad protection and attempted to foreclose others from patenting a composition with no separating layer by a uninformative comment as to such a possibility. However, Depui fails to describe how such useful and stable enteric coated dosage forms can be made without separating layer(s).

It is submitted that referring to a possible embodiment as "optional" is not a disclosure or description of embodiments employing or failing to employ the "option". This is especially true where, as here, the specification contains no written description of such an embodiment, no enabling disclosure of how to make or use the "optional" embodiments and, not only fails to provide a best mode, but fails to disclose any mode.

A mere mention of a possible embodiment is not sufficiently definite or particular that, without undue experimentation, one of ordinary skill in the art can gain possession of the claimed subject matter. See, Sheppard, supra, at page 45. Characterizing a feature as "optional" does not convey to one of ordinary skill in the art that the inventor had possession of that option or all other options. Accordingly, the Depui disclosure is not enabling to prepare stable and useful proton pump inhibitor oral dosage forms without having at least a separating layer. Hence there can be no anticipation.

During the June 10, 2003 interview, the Examiners indicated that they were not maintaining that Depui disclosed a stable dosage form without a separating layer but only that one could follow the Depui examples and just omit the steps leading to the inclusion of the separating layer. Such literalism undermines the requirement that a reference contain an enabling disclosure.

Since Depui never exemplifies an embodiment without a supporting layer, there is no basis in the record to believe such an embodiment would be successful. Accordingly, the Examiner is called upon to comply with the provisions of 37 C.F.R. 1.104(d)(2).

Claims 1 to 13 and 15 to 40 have been rejected under 35 U.S.C. 103(a) as unpatentable over Depui in view of comments set forth in the Official Action on page 4 thereof. However, the Examiner after discussing the disclosure of Depui concludes that one of ordinary skill in the art would have been motivated to make an oral composition comprising an inert core, an active coating, and an enteric coating without the presence of a separating layer based on the reference and the expected result would be a successful composition for the treatment of gastrointestinal disorders. However, the Examiner never sets forth what criteria or what basis there is to believe that the resulting composition would be "successful". Applicants have submitted extensive material showing that one would have expected to the contrary, that is in the absence of the separating layer, that the composition would not be "successful" whatever is meant by that term as employed by the Examiner.

To the contrary, based on the submissions, one would have expected failure. This is because as discussed above, Depui does not contain a single example that prepares such a composition and contains no information as to how such a composition would actually perform and relevant art discussed below teaches that the supporting layer is necessary. Curiously, Depui does not even include stability information in the formulations of the 14 examples. The request for compliance with 37 C.F.R. 1.104(d)(2) is repeated.

Claims 1 and 35 have been rejected under 35 U.S.C. §103 as unpatentable over Depui in view of Lovgren et al., EP 0 244 380 B1. It is submitted the rejection is improper and should be withdrawn.

The Lovgren reference teaches the necessity of the separating layer. Therefore, to combine this reference with Depui is improper since a vital and important part of the Lovgren reference would have to be disregarded. Clearly, the Examiner is engaging in a pick and choose technique to formulate an obviousness rejection based on hindsight reconstruction. This is improper under 35 U.S.C. §103. Also see In re Ratti 123 U.S.P.Q. 349 (CCPA, 1959).

Applicants submit there is a sufficient side by side showing of record by the comparison of the U.S. 6,132,771 examples with the examples of '505 patent.

Applicants have previously submitted a chart comparing example 9 of the '771 patent with Examples 7, 8 and Comparative Example V of the '505 patent. A comparison of the method to produce magnesium omeprazole pellets of the Example 9 of the '771 patent and the method to produce the pellets of Examples 7 and 8 of the '505 show that the processes are identical in those references. See previously submitted **Annex 2**. (Amendment of June 26, 2003).

The core material of Example 9 of the '771 patent has the same ingredients as the core material of Example 7 ('505 patent), the only difference being the ratio of magnesium omeprazole versus diluents, which is higher in Example 9. In both cases the core material is covered with hydroxypropylmethylcellulose and the percentage of the polymeric film forming material used in the separating layer is essentially the same (11 and 10% respectively).

Finally, pellets covered with a separating layer are further covered with an enteric polymer and the ratio of that polymer used in the enteric layer in both cases are essentially the same (11 and 10%, respectively). In order to calculate the % of methacrylic acid copolymer, one can assume that the material used is 100g of a 30% aqueous suspension of the polymer.

The formulation of Example 8 of the '505 patent is the same formulation of Example 7, wherein part of the mannitol diluent has been substituted by magnesium hydroxide.

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As stated in column 13, lines 40 to 65 of the '505 patent, the formulation of the Comparative Example V is the same as in Example 8 but no subcoating layer is used and the pellets are prepared as described in Example 2.

Annex 3 of the June 2003 Amendment is a chart comparing Example 14 of the '771 patent with Examples 2, 3, 4 and Comparative Examples I, II and III of the '505 patent.

Example 14 of the '771 patent shows an omeprazole formulation identical in respect to the core material to those of Examples 2, 3 of the '505 patent and substantially similar to that of Example 4 of the '505 patent. In the latter example, sodium lauryl sulphate has been replaced by a different but also well known surfactant, Pluronic F 68. In Example 14 ('771 patent) the core material is further coated with a film coating polymer (hydroxypropylcellulose) used in a ratio of 8% whereas in Examples 2, 3 and 4 ('505 patent), the film forming coating polymer (hydroxypropyl methyl cellulose or polyvinylpyrrolidone) is used in a 4 or 6% ratio.

Finally, in all the above cases, pellets with a separating layer are further coated with an enteric polymer used in an 8-10% ratio.

Again, the method to prepare omeprazole formulations of Example 14 of U.S. 6,132,771 and of Examples 2, 3 and 4 of the '505 patent is the same.

The formulations of Comparative Examples I, II and III are identical or substantially similar to those of Examples 2, 3 or 4 ('505 patent) but lack the separating layer.

Table 5 (column 14, lines 18 to 41 of the '505 patent) lists various parameters such as acid resistance and storage stability of the Examples 2 to 8 preparations (formulations with separating layer) and of Comparative Example I-V preparations (without separating layer). This comparison shows stability problems or unacceptable low resistance to dissolution in acid media, whereas the preparations with a separating layer have good gastric juice resistance and stability (see column 14, lines 64-68 and column 15 lines 1 to 31 of the '505 patent).

All example pellets of the '771 patent have a separating layer. Some of the examples of the '771 patent are identical or very close to the preparations of the '505 patent. In the '505 patent, there is a side by side comparison of preparations with and without a separating layer and it is well established that those lacking separating layer have problems. The '771 patent does not give any information as how to avoid the stability and acid resistance problems of the formulations lacking separating layers and therefore, one of skill in the art would not be encouraged or expect from the '771 in view of the '505 to prepare a stable formulation lacking a separating layer.

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Therefore, the stability difference in the Depui formulation where the drug dosage form is prepared with and without a separating layer has already been established by the '505 patent which is of record

During the course of the June 10, 2003 telephone interview, Applicant's undersigned counsel discussed using the above comparison to show that the disclosure of the Depui was insufficient and that one ordinary skill in the art could not, based on the Depui reference achieve a stable product. It is submitted that the above showing is sufficient. See *In re Fouche* 169 U.S.P.Q. 429, 433 (CCPA 1971).

The above comparisons were again discussed with the Examiner during the November 6, 2003 telephone interview. The Examiner inquired why the now claimed dosage form does not degrade as does Comparative Example III of the Lovgren Patent ("the '505 patent"). She also stated that she did not see a difference between the dosage form described in the Lovgren '505 patent or the Depui reference, and the now claimed invention.

The now claimed dosage form without a separation layer between the active containing layer and the enteric coating is stable because the active layer is homogeneous and non-porous. See pending claims 1, 34 and 36. The active containing layer is non-porous homogeneous and since all the coating steps are performed in a single fluidized bed coater of the Wurster type or the like.

This feature has been disclosed in the originally stated specification.

Page 2, lines 12-19 of specification reads as follows:

Numerous techniques recently have been developed for preparing systems of release in the form of microgranules wherein the mixture of active ingredient and excipients is submitted to a process of kneading, extrusion, spheronization, coating, etc. Each of these pelletization techniques calls for a different technology, so that there are many types of pelletization equipment, coating pans or drums, fluid-bed equipment, extruders-spheronizers and centrifuging equipment, among others. The final result would appear to be the same, although there are in fact considerable differences between the pellets made using each technique. (underlining added)

Page 7, lines 1-5, states:

In the present invention a formulation and a working methodology in a fluid bed of the "Wurster" type or the like have been developed. In it, the negative factors which affected the methods described to date are eliminated and substantial changes introduced with respect to the methods of previous patents for pellets containing benzimidazoles.

Page 8, lines 15-17, points out that:

The new galenical formulations object of the present invention are characterized in that they are spherical granules with a homogeneous active charge layer and a very unporous surface, formed by coating of an inert nucleus by spraying a single aqueous or hydroalcoholic mixture containing the active ingredient (anti-ulcer compound) together with the other excipients.

Page 9, lines 19 to 21, reads as follows:

When a single suspension-solution is projected onto the inert nucleus, a less porous and more homogeneous product is obtained than in the procedures known to date, and all the subsequent operations are simplified considerably. (Underlining added)

Also, on page 22 lines 1-2 and page 25, lines 13-14, it is disclosed that Photographs 4 and 8 show the low porosity and homogeneity of the coatings and the lack of pores accounts for the enhanced physical stability of the pellet.

Since the process is conducted in a single "Wurster" type fluidized bed coater, the claimed process need not encompass using other pieces of equipment different from fluidized bed coaters of the Wurster type or the like.

Neither Lovgren nor Depui teaches the substantially spherical, stable oral formulation claimed of the present invention having a non-porous, homogeneous active layer, or how to produce them, or a process whereby such a product is obtained.

Neither Lovgren nor Depui teaches that the homogeneous, nonporous characteristics and substantially spherical shape of the granules comprising an inert core and active coating layer are result effective parameters which influence the stability of benzimidazole containing pellets.

Lovgren and Depui disclose preparation of pellets wherein the benzimidazole core material are made by extrusion/spheronization (see Examples 2 to 8 and Comparative Examples I to V of Lovgren and Examples 9 and 14 of Depui).

Extrusion spheronisation is a multi-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheroniser to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution.

Lovgren teaches that these extrusion/spheronization benzimidazole containing cores having a separating layer beneath the enteric coating, have good resistance to gastric juice as well as good stability whereas the same formulation lacking a separating layer (those of Comparative Examples I to V) experience at least one of stability problems or poor resistance to dissolution in acid media.

Depui also discloses the preparation of pellets by the powder-layering technique using a centrifugal fluidized coating granulator. See Depui Example 10. These pellets have a separating layer between the core material and the enteric coating.

An example of benzimidazole containing core prepared by powder-layering technique using a

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centrifugal fluidized coating granulator with enteric coating layer but lacking the separating layer is disclosed in Example 6 of Takeda's EP 642797 ("Takeda '797"):

Example 6

Production of a formulation comprising lansoprazole and a gastrointestinal mucosa-adherent solid preparation containing AMOX

1) Granules containing lansoprazole was prepared as follows.

| Ingredients | mg |
|--------------------------------------------------------------------|-------|
| Lansoprazole | 30 |
| Magnesium Carbonate USP | 22.4 |
| Sugar Spheres NF | 110.0 |
| Sucrose NF | 59.8 |
| Starch NF | 36.4 |
| Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31) | 40.0 |
| Hydroxypropyl Cellulose NF (HPC-L) | 1.4 |
| Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.) | 44.6 |
| Polyethylene Glycol NF (PEG-6000) | 4.4 |
| Titanium Dioxide USP | 4.4 |
| Polysorbate 80 NF (Rheodol TW-0120) | 2.0 |
| Talc USP | 14.0 |
| Colloidal Silicon Dioxide NF (Aerosil) | 0.6 |
| Purified water * USP | q.s. |
| Total | 370.0 |

*: Removed during the manufacturing process

USP: The United States Pharmacopeia

NF: The National Formulary

Sugar spheres was coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrifugal fluid-bed granulator (CF-1000S, Freund Co.), and the resultant wet granules were dried in a vacuum oven at about 40°C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (F10-Coater FLO-60, Freund Co.), and sieved, and then dried in a vacuum oven at about 42°C for about 18 hours. The obtained granules were mixed with talc and Aerosil.

2) 370 mg of granules containing lansoprazole as obtained in 1) above and 100 mg of gastrointestinal mucosa-adherent solid preparation containing AMOX as obtained in Reference Example 3 were packed in No.0 capsules to yield a capsule preparation.

The previously submitted Declaration by Dr. Molina, Mr. Picornell and Mr. Bravo ("the Picornell Declaration") sets forth the attempts to reproduce Example 6 of Takeda '797. This experimental work led to the following conclusion:

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"Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastroresistant granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO 99/06032, particularly as described in example 1 therein."

Therefore, when enteric-coated gastroresistant benzimidazole granules are made by powder-layering technique using a centrifugal fluidized coating granulator without a separating layer between the active layer and the enteric coating, it results in granules having stability problems and unacceptable low resistance to gastric fluid. See Paragraph No. 5 of the Picomell Declaration.

This kind of powder-layering process is carried out in a centrifugal bead granulator, shown below schematically:

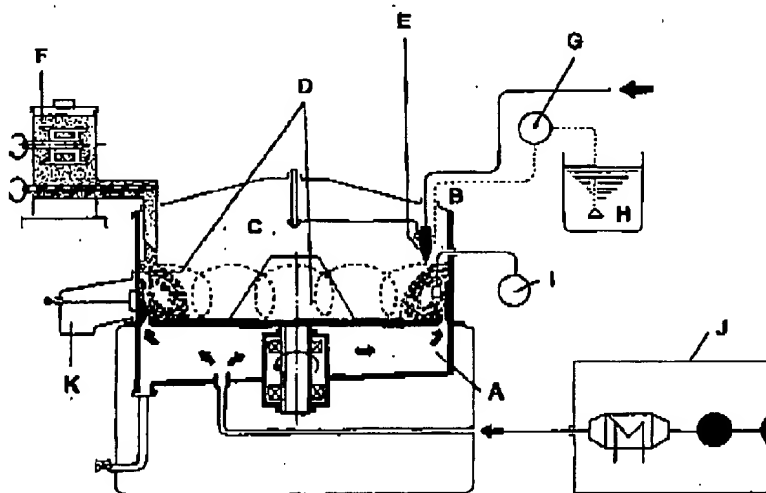


Figure 2. Schematic diagram of the centrifugal granulator. Key: Inlet air (A), Outlet air (B), Granulation chamber (C), Rotor (D), Solution spray system (E), Powder feeder (F), Liquid pump (G), Liquid vessel on a balance (H), Moisture sensor (I), Blow air generator system (J) and Product outlet (K) (modified from Goodhart 1989).

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See Attachment 1 hereto consisting of selected pages of an Academic dissertation or "Centrifugal granulation process for preparing drug-layered pellets based on microcrystalline cellulose beads", held at the University of Helsinki on April 2001. The complete text of the dissertation can be downloaded from:

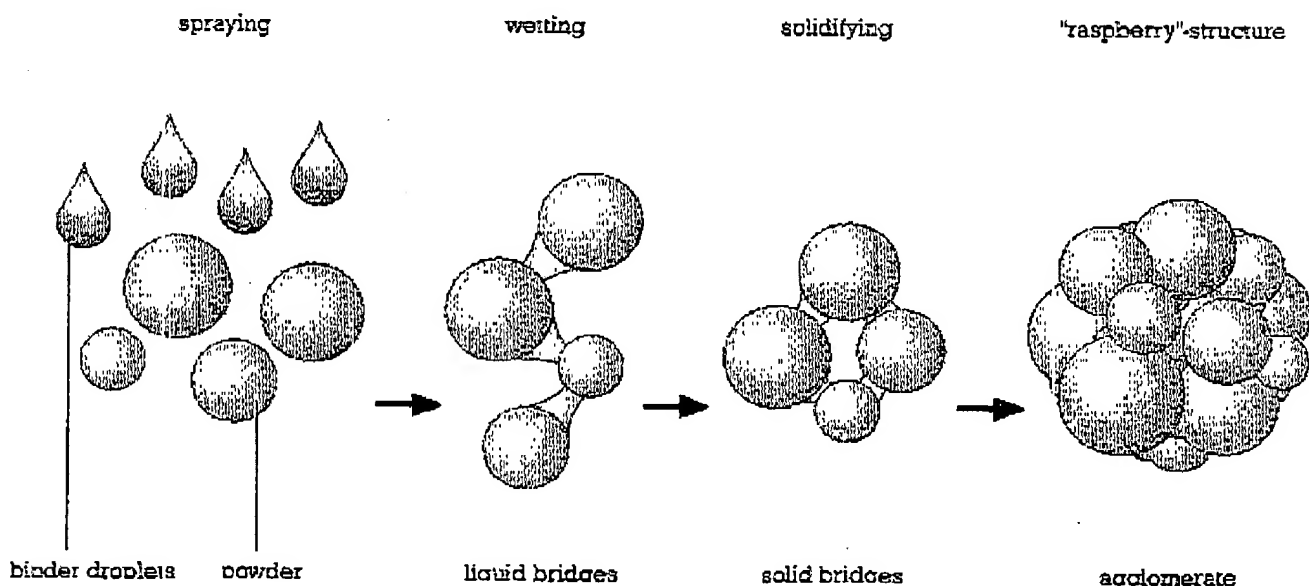
<http://ethesis.helsinki.fi/julkaisut/mat/farma/vk/rashid/centrifugal.pdf>

The schematic depicts a laboratory scale centrifugal fluid-bed granulator Freund CF-360EX, Freund Industrial Co., similar to the centrifugal fluid-bed granulator CF-1000S Freund Co. used in the Example 6 of Takeda '797.

As can be observed in the schematic, the beads are placed in a granulation chamber provided with a rotating plate at the bottom. The rotating plate centrifugally displaces the granules towards the chamber-wall, while the air flows by the plate edge. Simultaneously, the powder mixture is dosed from a powder feeder and the binding solution from a liquid vessel, producing a granulation process.

According to Takeda '797 Example 6, the granules after drying in an oven, are provided with an enteric coating by a subsequent coating process carried out in a fluidized-bed coater.

Applicant has already submitted technical trials which prove that by using the above process it is not possible to obtain pharmaceutically acceptable two-layered pellets, and this may very well be due to the structure of the resulting active coated pellets having a "raspberry" type structure, that is a porous, non-compact, non-homogeneous, open surface.



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However, in the present invention the inert nuclei are coated with a single solution-suspension containing the active ingredient, the binder and the other excipients of the first active containing layer, by using a single fluidized-bed coater.

As disclosed in the present application appropriate fluidized-bed coaters are, for example, those of Wurster type or similar. In the Wurster process, the inert nuclei to be coated are fluidized in an upward-moving airstream. A high-velocity airstream is introduced into the fluidized bed, causing a spout. A draft-tube partition is placed around the spout to prevent the beads in the spout from colliding with the particles descending in the fluidized bed. A cyclical flow of particles is thus created. When beads enter the high-velocity spout, they are uniformly accelerated and physically separated from each other. As the high-velocity air and the beads move up, the solution-suspension for coating is applied by a spray nozzle mounted at the base of the spout. The process air that moves the beads also serves to dry the coating. Because of the large amounts of air used, excellent drying is obtained. When the airstream and particles clear the top of the partition, the air in the spout spreads out to fill the expansion chamber, and the beads settle out on the top of the bed of fluidized beads. Because the bed of particles is fluidized by air, additional drying occurs as the beads descend to the bottom of the bed and re-enter the partition, where they are accelerated again by the high-velocity airstream and receive additional coating.

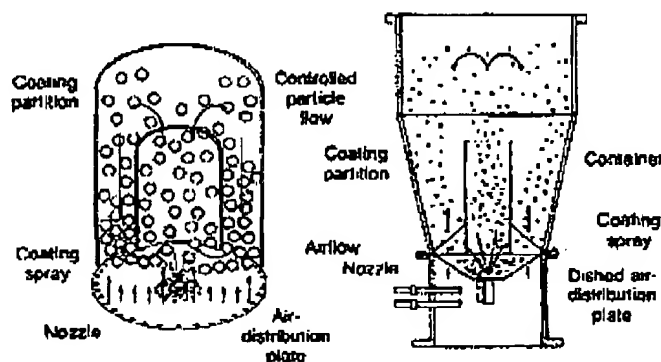


Figure 7: A standard Wurster chamber with a flat bottom plate and a container with a dish distributor plate.

See Attachment 2. "Airflow in batch fluid-bed processing", downloaded from:

<http://www.niroinc.com/html/pharma/pairflowarticle.html>

at the web page of Niro Inc., the manufacturer of the Wurster type fluidized-bed coater used in Examples 1 and 2 of the present application.

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After the coating with the active layer, the enteric coating is applied to the pellets in the same fluidized-bed coater.

Accordingly, the product and process of the present application does not encompass the extrusion/spheronization technique nor the powder layering process, because it does not refer to a granulation process for agglomerating different kind of solids in particulate or powdered form, but to a pure coating process with a single coating homogeneous solution-suspension. Thus, the pellets obtained are different in structure and properties from the pellets or the core material according to the other processes.

The structure of the pellets of the present invention accounts for the compactness, non-porosity, homogeneity, closed surface of the particles and, as a consequence of that, its stability.

Depui Examples 1, 3, 4, 5 and 11, refer to the formation of pellets by suspension layering in a fluid bed apparatus but it is clear from the specification (col. 9, ll. 57 et. seq.) that Depui sees no relationship between any particular layering technique or conditions and the stability or gastric resistance of the resulting product.

An objective achieved by the present invention is a more simple and efficient process to obtain two-layered benzimidazole anti-ulcer pellets in form of substantially spherical granules provided with a homogeneous non-porous active charge layer and an outer enteric layer, which are uniform and well shaped, having good friability and which are stable for an acceptable time period. See the present specification at pages 20, 24 and 25.

The solution proposed consists of coating the inert nuclei with a single solution-suspension containing the active ingredient, the binder and the other excipients of the first layer and, after drying, providing the obtained pellets with a second enteric layer, the coating operations being performed in a single Wurster type or similar fluidized-bed coater.

As explained in the first page of the present application there are many techniques to prepare microgranules and multi-layered pellets and there are also many types of pelletization equipment.

Since neither Lovgren nor Depui teaches that the stability of pellets containing benzimidazoles could depend on the homogeneous, nonporous characteristics and spherical shape of the granules comprising benzimidazole and that enteric coated benzimidazole containing granules lacking a separating layer or the coating technique and both patents fail to recognize that granules made either by extrusion/spheronization or by powder layering techniques have stability problems and/or unacceptable low resistance to gastric fluid, one of ordinary skill in the art would not be motivated to prepare stable two-

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layered benzimidazole anti-ulcer pellets by selecting a suspension layering method using a "fluid bed apparatus" as generically disclosed in examples 1, 3, 4, 5 and 11 of the '771 patent.

Without an inventive effort the skilled person would not be motivated to use the claimed process or have any reasonable expectation of success.

As indicated on page 1 of the Attachment 2, significant amounts of solid material are processed using fluid-bed technology and one primary factor influencing a fluidized-bed process is airflow. Figure 1 of Attachment 2 shows the typical components of a fluid-bed processing unit. A fluid bed is a bed of solid particles with a stream of air or gas passing upwards through the particles at a rate great enough to set them in motion. Different types of bed are formed depending upon the movement of bubbles through the bed. See for instance, Example 3 of Attachment 2.

There are many kinds of fluidized bed apparatus. On page 4 of Attachment 3 (document downloaded from http://www.glatt-weimar.de/download/konti_ws_en.pdf), there is an example of a fluid bed useful for building up particles from powder-agglomeration or for liquid-granulation and to coat particles. All these processes can be accomplished by selecting air with different velocities in different chambers, selecting air temperatures and by the correct placement of the nozzles in the fluid bed.

None of the examples of the '771 discloses the use of a Wurster type or the like fluidized bed coater. The selection of this type of fluid bed equipment allows strict and automated control of the spraying and drying conditions necessary to apply the two layers to the inert core.

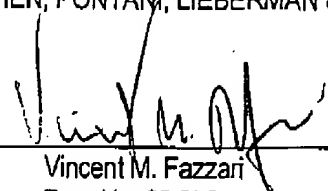
Reconsideration and allowance of the application with claims 1 to 13 and 15 to 40 are requested.

The Examiner is reminded that she advised that Applicant should call following submission of this response.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

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Dated: December 12, 2003

ATTACHMENT
4

Pharmaceutical Technology Division
Department of Pharmacy
University of Helsinki
Finland

**Centrifugal Granulating Process for Preparing Drug-
Layered Pellets Based on Microcrystalline Cellulose
Beads**

Md. Harun Ar Rashid

Academic Dissertation

To be presented with the permission of the Faculty of Science of the University of Helsinki,
for public criticism in Auditorium 2041 of Biocentre Viikki,
on April 20th, 2001 at 12 noon

Helsinki 2001

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3. EXPERIMENTAL

3.1 Materials

For preparing spherical microcrystalline cellulose (MCC) beads, Emcocel 90M (NF, JP, Ph.Eur., E. Mendell, Finland) was used as initial seed material (I, II). As fillers, Emcocel 90M, 50M (NF, JP, Ph.Eur., E. Mendell, Finland) HD90 and SM15 (NF, JP, Ph.Eur., E. Mendell, United States) were used (I, II). Purified water (Ph.Eur.) was used as a wetting agent.

Drug-layered pellets (III, IV) were prepared by using MCC beads previously prepared in the centrifugal granulator as substrates. The bead size fraction used was 355-1000 μm . Povidone and maltodextrin were used as aqueous binding agents. Povidone is a widely used binder studied both for granule and pellet preparation (Ghebre-Sellassie et al. 1985, Knop and Lippold 1989, Robinson and Hollenbeck 1991, Niskanen et al. 1992). Two grades of Povidone (Plasdone K-29/32 and K-25) at concentrations of 12%, 16%, 18% and 20%, (w/w) were studied. Maltodextrins are water-soluble hydrolysed starches commercially available in different grades. They differ mainly due to their DE (dextrose equivalent) values. The maltodextrin grades used were Maltrin M040 and M100 at concentrations of 12%, 16% and 20% (w/w).

As a model drug and solvent, previously milled sparingly water-soluble caffeine anhydride (Ph.Eur.) and purified water (Ph.Eur.) were used, respectively (III, IV).

3.2. Equipment

A laboratory-scale centrifugal granulator (Freund CF-360EX, Freund Industrial Co., Ltd., Tokyo, Japan) was used for preparing both MCC beads and subsequent drug-layered pellets (I-IV). The schematic diagram of the equipment is presented in Figure 2. The principal units of the equipment are as follows:

a) *Product processing chamber* - The chamber (marked C in Figure 1) consists of a fixed cylindrical stator and a non-perforated rotating disc (D). The speed of the disc is controlled by a variable-speed rotor attached to the bottom. The fluidized air (A) enters the product area through the slit between the chamber and the rotating disc which is 0.2 mm. The dust accumulation during the operation is minimised by a cover and outlet air tube (B). The cover has openings to allow the position of clamp assembly, tubings of the spray guns and a powder delivery tube within the chamber. The product temperature and moisture are monitored by probes positioned just above the rotating disc (I).

b) *Powder feeding device* - This device (F) is situated over the processing chamber and consists of a vertical feed screw, a hopper and a hopper agitator. The rotation speed of the screw controls the powder dropping rate.

c) *Liquid spray assembly* - The assembly has two main units: 1) an exchangeable speed flow gear pump (G) situated near the processing chamber and 2) a spray gun (E), the position and angle of which can be altered as desired by means of a clamp unit. The binders and coating solutions of different viscosities are delivered suitably with the gear pump. The liquid is atomised by using air pressure through the spray gun which is usually of a binary type.

d) *Air supply system* - Air supply into the processing chamber is maintained by a blower (J). The blower air is supplied through a heat exchanger into the air chamber below the processing chamber and then entered in the process chamber via the slit (A). The function of the air is to facilitate the drying, to enhance the motion as well as to prevent the blocking of the slit during the processing of fine granules.

e) *Control panel* - It consists of (1) a basic control panel with on-off switches, pilot lamps, a thermometer and rotation speed meters, and is designed, on production units, for remote locating and (2) optional moisture feed back control panels that optimise agglomeration and granulating times by controlling the moisture content of the bed during agglomeration.

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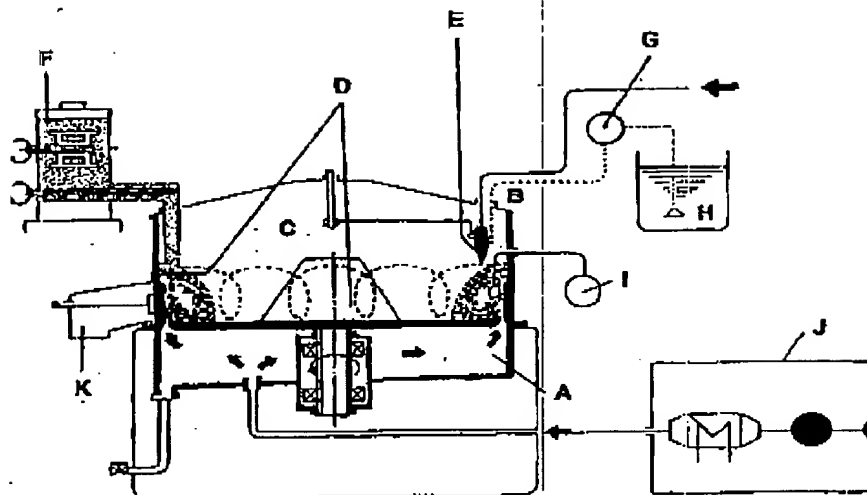


Figure 2. Schematic diagram of the centrifugal granulator. Key: Inlet air (A), Outlet air (B), Granulation chamber (C), Rotor (D), Solution spray system (E), Powder feeder (F), Liquid pump (G), Liquid vessel on a balance (H), Moisture sensor (I), Blow air generator system (J) and Product outlet (K) (modified from Goodhart 1989).

3.3. Methods

3.3.1 Characterisation of materials

Moisture content (I, III)

Moisture content was determined as the loss of weight using an infrared dryer (Sartorius Thermocontrol YTC01L, Sartorius GmbH, Germany). A 2-g sample was heated up to 120 °C until the loss of weight was less than 0.1 mg in 50 s. Three parallel determinations were performed in each case.

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Airflow in Batch Fluid-Bed Processing

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Significant amounts of solid materials are processed using fluid-bed technology. Suspension and movement of particles in an airstream maximizes the exposure of particle surfaces to air or gas, producing efficient evaporation. The primary factor influencing a fluidized-bed process is airflow. To understand and manipulate processing in a fluid bed, it is important to learn how airflow is generated, conditioned, and distributed through the bed during drying, agglomerating, and coating. This article describes how uncommon pressure drops and related processing problems can be identified and notified by studying the airflow of the system.

The batch fluid-bed processor is used to perform drying, agglomeration, mixing, and coating operations. In the last 30 years, the popularity of the fluid-bed processor has expanded as manufacturers have provided different ways to control airflow through the unit. Sophisticated controls, computer systems that monitor process parameters, and air handlers equipped with temperature and humidity controls are some of the innovations that have increased the range of applications for batch fluid-bed processing. Figure 1 shows the typical components of a fluid-bed processing unit.

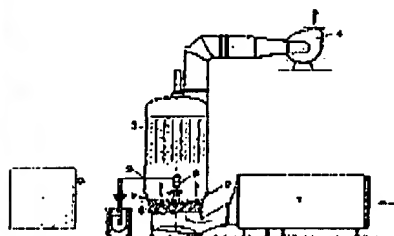


Figure 1: Typical components of a fluid-bed processing system
1 = air preparation unit; 2 = product container; 3 = exhaust filter; 4 = exhaust blower; 5 = control panel; 6 = air distribution plate; 7 = product; 8 = spray nozzle; 9 = solution delivery.



Figure 2: An incipiently fluidized bed.

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate great enough to set them in motion.

An expanded bed is formed when the gas or airflow rate increases and particles move apart. A few visibly vibrate and move about in restricted regions. At still higher velocities of airflow, all the particles become suspended. At this point, the frictional force between a particle and air balances the weight of the particles, the vertical component of the compressive force between adjacent particles disappears, and the pressure drop through any section of the bed approximates the weight of air and particles in that section. The bed is referred to as an incipiently fluidized bed or a bed at minimum fluidization. This is illustrated by Figure 2. With an increase in airflow rates beyond minimum fluidization, large instabilities with bubbling and channelling of air create different types of beds (Figure 3).

Airflow in Batch Fluid-Bed Processing

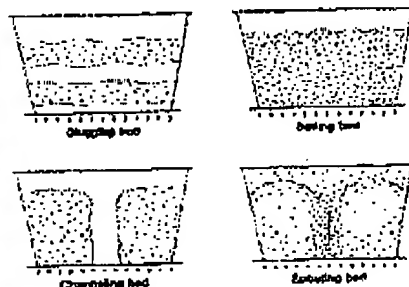


Figure 3: Different types of fluidized beds.

A slugging bed is a fluid bed in which air bubbles occupy entire cross sections of the vessel and divide the bed into layers.

A boiling bed is a fluid bed in which the air or gas bubbles are approximately the same size as the solid particles.

A channeling bed is a fluid bed in which the air (or gas) forms channels in the bed through which most of the air passes.

A spouting bed is a fluid bed in which the air forms a single opening through which some particles flow and fall to the outside. At higher airflow rates, agitation becomes more violent and the movement of solids becomes more vigorous. Additionally, the bed does not expand much beyond its volume at minimum fluidization. Such a bed is called an aggregative or bubbling fluidized bed (Figure 4). At sufficient airflow rates, the terminal velocity of the solids is exceeded, the upper surface of the bed disappears, entrainment becomes appreciable, and the solids are carried out of the bed with the airstream.

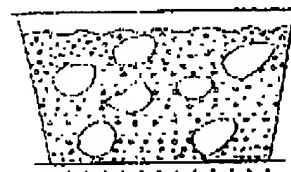


Figure 4: A bubbling bed.

EFFECT OF AIRFLOW THROUGH THE BED

As the air travels through the particle bed, it imparts unique properties to the bed. For example, the bed behaves like a liquid. It is possible to propagate wave motion, which creates the potential for improved mixing. The surface area of fluidized particles is large, which improves heat transfer, reduces process time, and imparts reproducible operating parameters. In a bubbling fluidized bed, no temperature gradient exists within the mass of the fluidized particles. This isothermal property results from the intense particle activity in the system. Thus, the fluid bed can be used to agglomerate particles, improve flow properties, instantize the product, produce coated particles, pellets, or tablets, taste-mask bitter products, or effect uniform chemical reactions in a controlled fashion.

GAS-BUBBLE THEORY

When product is fluidized by a gas, the frictional force between gas and particles counterbalances the weight of the particles. Because of the viscous drag on the particles, a pressure drop across the bed occurs and is proportional to the weight of the bed. When the pressure drop is equal to the gravitational force acting on the particles, the bed is just fluidized and the gas velocity is called *minimum or incipient fluidization velocity*. Davidson et al. have shown that the minimum fluidization velocity is a function of the square of the particle diameter and the difference between particle density and gas or air density.¹ As a result, the quantity of air required for minimum fluidization changes as the product's particle size or density changes.

The mechanisms by which air affects fluidization have been discussed by various researchers.^{2,4} When the fluidizing velocity is greater than the incipient velocity, bubbles of air rise through the bed. Initially, small bubbles form at the distributor plate. These small bubbles tend to join together or coalesce as they rise through the bed. This creates larger and fewer bubbles than those near the distributor plate.

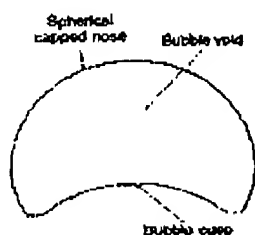


Figure 5: A typical gas bubble shape.

Figure 5 shows a typical gas bubble shape. Gas bubbles have a spherical cap and an indentation at their rear, known as the cusp. The cusp is associated with the bubble wake.

To demonstrate the effect of the bubble wake, Rowe et al. used x-ray photographs of bubbles rising through a bed composed of a lower layer of lead-glass beads and an upper layer of soda-glass beads.⁵ The photographs showed that as a bubble rose through the upper layer, it took with it a wake composed of material from the lower layer.

Mixing does not generally occur when the bed is fluidized at very low or zero excess-gas velocities, because insufficient bubbles are formed to cause bulk displacement of particles. Typically, the proportion of bubble volume V_b to wake volume V_w is about 3:1 (Figure 6).

Airflow in Batch Fluid-Bed Processing

In summary, the most important single factor in a fluidized system is gas velocity. It is the gas passing through the system in the form of bubbles that determines the degree of mixing. The extent of mixing appears to vary with particle size. Mixing of particles having a mean particle size of less than approximately 150 μm decreases as the mean size approaches zero.

Different types of beds are formed depending upon the movement of bubbles through the bed. For example, slugging (Figure 3) occurs in a bed that has a height-to-diameter ratio >1 , where bubble diameters may begin to approach half the bed diameter and form a slug. Because of wall effects, the slug will rise more slowly than a bubble, and further growth of the bubble occurs by vertical elongation. The pattern of movement of gas phase in and out of a bubble depends on several factors, including minimum fluidization velocity and particle size. These movements affect heat transfer between air (bubbles) and the particles. This simple representation is complicated in practice by factors such as non-sphericity of the bubbles, presence of wake, other bubbles, and wall effects.

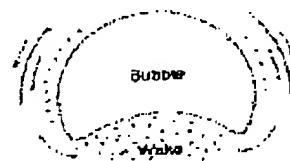


Figure 5: The ratio between bubble volume and wake volume is typically 3:1

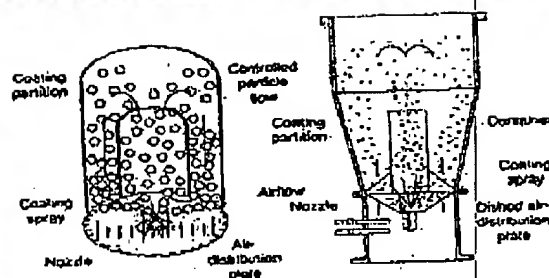


Figure 7: A standard Wurster chamber with a flat bottom plate and a container with a dish air-distributor plate.

When particles, beads, or tablets enter the high-velocity spout, they are uniformly accelerated and physically separated from each other. As the high-velocity air and the particles move up, the coating is applied by a spray nozzle mounted at the base of the spout. The process air that moves the particles also serves to dry the coating. Because of the large amounts of air used, excellent drying is achieved by this process. When the airstream and particles clear the top of the partition, the air in the spout spreads out to fill the expansion chamber, and the particles settle out on the top of the bed of fluidized particles. Because the bed of particles is fluidized by air, additional drying occurs as the particles descend to the bottom of the bed and reenter the partition, where they are accelerated again by the high-velocity airstream and receive additional coating. Figure 7 shows a standard Wurster chamber with a flat bottom plate and a dish air-distributor plate in this container is designed to help particles, beads, or tablets enter the coating zone, thus facilitating uniform cyclical flow of the particles and subsequent uniform coating.

The spouted bed is a combination of a jet-like, upward-moving, dilute, fluidized phase, which is surrounded by a slow, downward-moving bed through which gas percolates upward. Whether or not a particle bed can be made to spout depends on gas flow, bed depth, inlet-nozzle diameter, and particle diameter. The spouted-bed principle was successfully implemented for coating in Wurster's 1959 invention. In the Wurster process, the particles or tablets to be coated are fluidized in an upward-moving airstream. A high-velocity airstream is introduced into the fluidized bed, causing a spout. A draft-tube partition is placed around the spout to prevent the particles in the spout from colliding with the particles descending in the fluidized bed. A cyclical flow of particles is thus created.

DISTRIBUTOR PLATE

As the conditioned air is introduced through the lower plenum of a batch fluid bed, the velocity of a given volume of air determines how fluidization will be achieved.

Air-distributor plates covered with a 60 mesh or finer screen provide an appropriate means of supplying air to the bed. Along with distributing the airflow, these plates also regulate the air. These plates are identified by their percentages of open area. Distributor plates that have 4%, 6%, 8%, 12%, 16%, and 30% openings are available. These interchangeable plates provide a range of loading capacities so that batches of various sizes can be produced efficiently and with uniform quality. To prevent channeling, an operator can select a plate with optimum fit properties. For example, a product with low bulk density requires low incoming-air velocity. A distributor plate having a large open area may provide uniform fluidization of such a product without shooting the product into the filter housing and plugging the filter. Alternatively, a more dense product can be fluidized and processed using a plate with smaller holes that provides more velocity for a given volume of air. A dish distributor plate is preferred because it facilitates the flow of product through the coating zone when a bottom-coating technique is used.

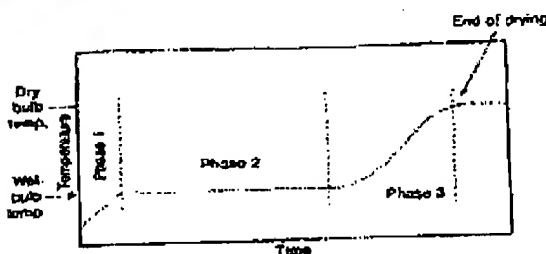


Figure 8: Temperature phases in the drying process.

DISTRIBUTION OF AIR

Because heated air is used to dry the product during the drying, agglomeration, and coating processes, the drying capacity of the air must be carefully monitored.

Airflow in Batch Fluid-Bed Processing

| Typical Outside Climatic Conditions | | Process Air Temp. | Typical Exhaust Air Conditions | |
|-------------------------------------|--------------------------------------------------|-------------------|--------------------------------|--------------------------------------------------|
| Temperature and Humidity | Moisture Content (g H ₂ O/kg dry air) | | Temperature and Humidity | Moisture Content (g H ₂ O/kg dry air) |
| 30 °C, 85% RH | 23 | 50 °C | 35 °C, 90% RH | 28 |
| 4 °C, 30% RH | 1.5 | 60 °C | | |
| 30 °C, 85% RH | 23 | 80 °C | 70 °C, 80% RH | 220 |
| 4 °C, 30% RH | 1.5 | 90 °C | | |

During fluid-bed drying, the product passes through three distinct temperature phases (Figure 8). At the beginning of the process, the material heats up from the ambient temperature to approximately the wet-bulb temperature of the air in the dryer. This temperature is maintained until the material's moisture content is reduced to the critical level. At this point, the material holds no free surface water, and the temperature starts to rise further. In some cases, the temperature continues to rise until it equals the temperature of the air in the dryer, but in most processes the drying is stopped before the material reaches this terminal temperature.

The drying capacity of the air depends upon the relative humidity (RH) of the incoming air. At 100% RH, the air is holding the maximum amount of water, but if the temperature of the air is raised, the relative humidity drops and the air can hold more moisture. If air is saturated with water vapor at a given temperature, a drop in temperature will force the air mass to relinquish some of its moisture through condensation. The temperature at which moisture condenses is the dew point temperature. Dew point and vapor pressure are directly related.

Thus, the drying capacity of the air varies significantly during processing. By dehumidifying the air to a preset dew point, one can maintain constant drying capacity and, hence, a constant process time. This is an expensive proposition, but more and more companies are opting for this to ensure product quality and process consistency.

When low-temperature fluidizing air is used, climatic conditions can play a significant role in the fluid-bed process. In geographic locations where the absolute humidity varies during the year, its effect on the relative humidity of the heated, fluidized air becomes pronounced. Table 1 shows the effect of outside conditions on process conditions. One approach, raising the inlet-air temperature, is limited by the product's heat sensitivity. Each degree of increase in the inlet temperature is less beneficial than is a corresponding decrease in the outlet-air temperature.

In a typical drying process, suspended particles in a concurrent airstream are kept relatively cool by evaporation. Thus, inlet-air temperature can be much higher than the product degradation point. However, if powder clings to equipment surfaces, it may scorch. Finding and maintaining the optimum difference (ΔT) between the inlet-air temperature and the wet-bulb temperature is cost-effective, especially for dryers with small ΔT (21 - 35° C).

Yet another approach is to reduce the outlet-air temperature. A unit volume of the cooler outlet stream carries more air by weight than does the warmer inlet airstream. Thus the outlet temperature has greater influence on energy use and productivity per degree of change. The lowest practical setting of outlet temperature significantly benefits energy and productivity and usually product quality. However, cooler outlet air raises humidity significantly, and this may restrict the allowable ΔT if product moisture is increased.

With certain resins and other heat-sensitive materials, longer residence time in the drying zone permits a lower outlet temperature without increased product moisture. Using a longer residence time has an effect similar to that of raising the outlet temperature. Uniform particle size has the same effect. When particles are nonuniform, larger ones need a higher temperature, a longer time to dry, or both.

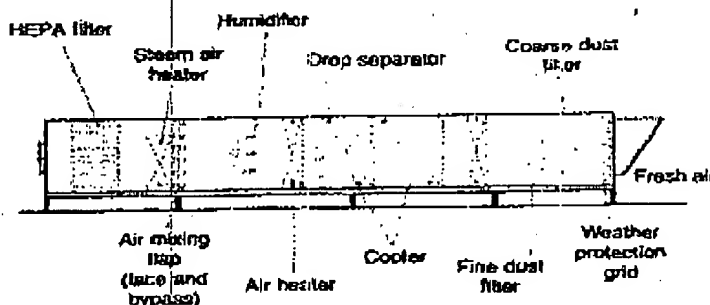


Figure 9: A typical layout of an air conditioning system.

AIR HANDLING SYSTEM

Airflow in Batch Fluid-Bed Processing

As the process air enters the fluid-bed unit's air-handling system, it can be heated, cooled, humidified, dehumidified, or filtered. A typical layout of an air-conditioning system is illustrated in Figure 9.

Filtration. Following a bird screen, a coarse dust filter is placed where the air enters the system. Additional filtration of the air after heating is achieved by the use of high-efficiency particulate air (HEPA) filters.

Dehumidification. A cooler followed by a droplet catcher dehumidifies the air.

Heating. Process air is usually heated by a finned-tube heat exchanger. The two most widely accepted methods of controlling temperature are modulating steam valves and a face and bypass airflow damper system used in conjunction with a flooded steam coil. The face and bypass system offers the advantages of precise temperature control ($\pm 1^\circ\text{C}$ or less) and the ability to change temperatures rapidly during the process with little or no offset.

Humidification. During cold and dry seasons, air humidity may actually be lower than desirable, and rehumidification may be necessary. A clean-steam injector can be used for this purpose after the cold and dry air is heated. Humidification is used primarily to maintain constant inlet conditions and process times.

In many processes, when preheating is required a bypass loop can be used for preconditioned air. This loop allows the required process temperature and humidity to be attained within the vessel before the product is subjected to fluidization.

HEAT AND MASS TRANSFER

In a fluidized bed, conditions for heat transfer are extremely favorable. A dry, packed bed of particles is generally a good thermal insulator because there is very little contact between adjacent particles; little heat flows by conduction, even when the thermal conductivity of the solid is high. Heat transfer by convection is also small because the motion of the interstitial gas is restricted by the particles. But in a fluidized bed, equilibrium is achieved because the particles at the wall are frequently replaced by particles from the interior of the bed. The high rate of mixing is caused by passing bubbles, which are essential to maintain heat transfer.

In the absence of a temperature probe, product temperature can be inferred. The equilibrium temperature for any surface from which water is evaporating adiabatically (i.e., without heat transfer from its surroundings) is the wet-bulb temperature. As water evaporates in the air, the dry-bulb temperature of the air falls and the humidity increases, but the heat content remains the same. In an adiabatic dryer, the wet-bulb temperature is the true temperature of the solid surface during this constant-rate period.

As in heat transfer, the maximum rate of mass transfer that occurs during drying is proportional to surface area, turbulence of the drying air, the driving force between the solid and the air, and the drying rate. Because the heat of vaporization must be supplied to evaporate the moisture, the driving force for mass transfer is the same driving force required for heat transfer, which is the temperature difference between the air and the solid.

PRESSURE

To move air in a fluid bed, blowers or exhaust fans mounted outside of the processing area impart motion and pressure to the air using a paddle-wheel action. The moving air acquires a force or pressure component in its direction of motion because of its weight and inertia. This force is called velocity pressure and is measured in inches or millimeters of water column (wc). In operating duct systems, a second pressure that is independent of air velocity or movement is always present. Known as static pressure, it acts equally in all directions. In exhaust systems (such as fluid beds), a negative static pressure will exist on the inlet side of the fan. Total pressure is the combination of static and velocity pressures.

Blower size is determined by calculating the pressure drops (ΔP) created by all the components of the completed system. For example, a 28-in. blower creates a pressure differential between the exhaust and inlet blower that is equal to the pressure at the bottom of a 28-in.-high water column.

The blower in a fluid-bed system discharges directly into the atmosphere, which is designated as having a pressure of zero (gauge). Therefore, a 28-in. blower creates a ΔP of 28 in. between the exhaust and inlet. However, because the exhaust has a pressure of zero, the blower has a negative pressure of 28 in. cf water. The ΔP created by the fan is dissipated by the equipment located in the system. Table II shows an example of the ΔP experienced by various pieces of equipment in a hypothetical situation.

The exhaust flap dissipates excess ΔP not needed to fluidize the material. This flap is controlled by a pneumatic positioner that allows an infinite number of settings. A blower with a suitable ΔP will fluidize the process material properly. However, a blower without enough ΔP will not allow proper fluidization of the material, resulting in a longer drying time. If the blower develops too much ΔP , the control of fluidization will be very difficult. A properly sized blower should develop ΔP so that the exhaust flap will be used in the 50 - 80% open position. When equipment such as scrubbers and duct filters is added, the ΔP of the blower can be increased to compensate for the additional resistance created in the system.

| Equipment | ΔP (in. wc) |
|--------------------------------------------|---------------------|
| Inlet rough filter | 0.5 |
| Heater housing | 0.5 |
| HEPA filter | 2 |
| Inlet plenum & bottom plate | 5 |
| Processing material | 4 |
| Filter bags | 7 |
| Exhaust explosion protective valve | 2 |
| Air duct | 0.5 |
| Capacity for processing & exhaust air flap | 0.5 |
| Total | 28 |

Airflow in Batch Fluid-Bed Processing

EXHAUST FILTER SYSTEMS

Containing all the product inside the fluid-bed system by using an exhaust air filter is one of the most important aspects of fluid-bed processing. The ideal filter material should retain all of the product particles in the container while allowing process air to pass through. Cotton, polyester, polypropylene, nylon, and expanded polytetrafluoro-ethylene (Gore-Tex, W.L. Gore & Associates, Elkton, Maryland, USA) are the most commonly used materials. These filters can be obtained in 1- to 25- μ m sizes. The particle size of the product being processed and the type of unit operation (coating, agglomerating, or drying) will dictate the level of porosity of the filter material that should be used. Because the filter can cause a significant ΔP , many process failures result from the selection of filter media that have openings of the wrong size. Process failures can also occur when the filter clogs because of excessive fluidization of fine powder or when filters are improperly cleaned during the process. Too fine a filter will impede fluidization, causing excessive ΔP , and a too-coarse filter will cause loss of valuable product carried by process air. Maintaining a large filter area ensures proper airflow and reduces ΔP due to impingement from overfluidization. Reduced-area or pleated filter media can be problematic, because the ΔP across the filter bag can increase with air speed.

PROCESS CONSIDERATIONS

Airflow in drying. One constraint in using a fluid-bed dryer is the inability to achieve uniform fluidization. An indication of good fluidization is a free downward flow of the granulation at the sight glass of the drying bowl, but such limited observation could be misleading. It is possible to detect this situation by monitoring the outlet-air temperature. Every product has a unique constant rate of drying period in which the bed temperature remains relatively constant for a significant length of time. Therefore, if the outlet-air temperature rises more rapidly than anticipated, it is an indication that fluidization is incomplete. In this case, the process must be stopped, the granulation stirred to distribute the moist material, and the process restarted.

Airflow in granulation. While the granulating solution is being sprayed, the exhaust flap is controlled to achieve proper fluidization. The objective of this process is to fluidize the powder for maximum exposure to the spray nozzle. Whereas overfluidization may produce uneven or lumpy agglomerates and may also cause filter plugging, underfluidization may stall the bed and ultimately lead to bed collapse. Filters can also become plugged.

Minimum fluidization velocity depends on particle size and particle humidity.⁴ As both change during the granulation process, it is necessary to vary the air velocity to maintain uniform fluidization. As the product dries, its density changes and less airflow is required.

The difference between the temperatures of the drying air and the product surface is expressed as ΔT . It is necessary to distinguish between ΔT in the granulation phase (ΔT^g) and ΔT in the drying phase. Granule size is directly proportional to the moisture content of the bed in the granulation phase. ΔT^g primarily affects granule growth. As the value of ΔT is increased, drying time is decreased. Variations in inlet-air humidity thus affect the granule size by either increasing or decreasing ΔT^g versus the drying capacity of the air changes. This influence can be eliminated by keeping the difference (ΔT) between the inlet-air temperature and the wet-bulb temperature constant.⁴

Airflow in coating. Tablet, pellet, and particle coating are all performed in fluid-bed equipment using a top spray, a bottom spray with a Wurster column, or a rotary coater. The coating process involves the deposition of droplets on the substrate material, followed by spreading and coalescing of the droplets, which form a continuous layer as they adhere to the matrix. Throughout the process, solvent is evaporating. It would be impossible to dry any more solvent than the drying air can accept or to dry any faster than the solvent can be heated to its vapor-transition temperature. In a system with good product turnover and proper exposure to spray, the one remaining requirement for successful coating is the drying system. If water is present in the organic solvent solution and dew points are not controlled, then the drying capacity varies, and the driving force for the evaporation of water is affected. It is advisable to control ambient air dew points in organic solvent processes and in aqueous coating operation.

CONCLUSION

The fluidized-bed unit is one of the most versatile pieces of production equipment in the process industries. A fundamental understanding of the mechanism of fluidization, normal pressure drops across various elements, the effects of variable climatic conditions, and heat and mass transfer during various unit operations will minimize the number of process problems encountered.

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4. V.I. Gorodnichenov et al., *Pharm. Chem. J. (USSR)* (English Translation) 8, 298 (1974).
5. T. Schoefer and O. Worts, *Arch. Pharm. Chem. Sci. Ed. B*, 1-13 (1978).

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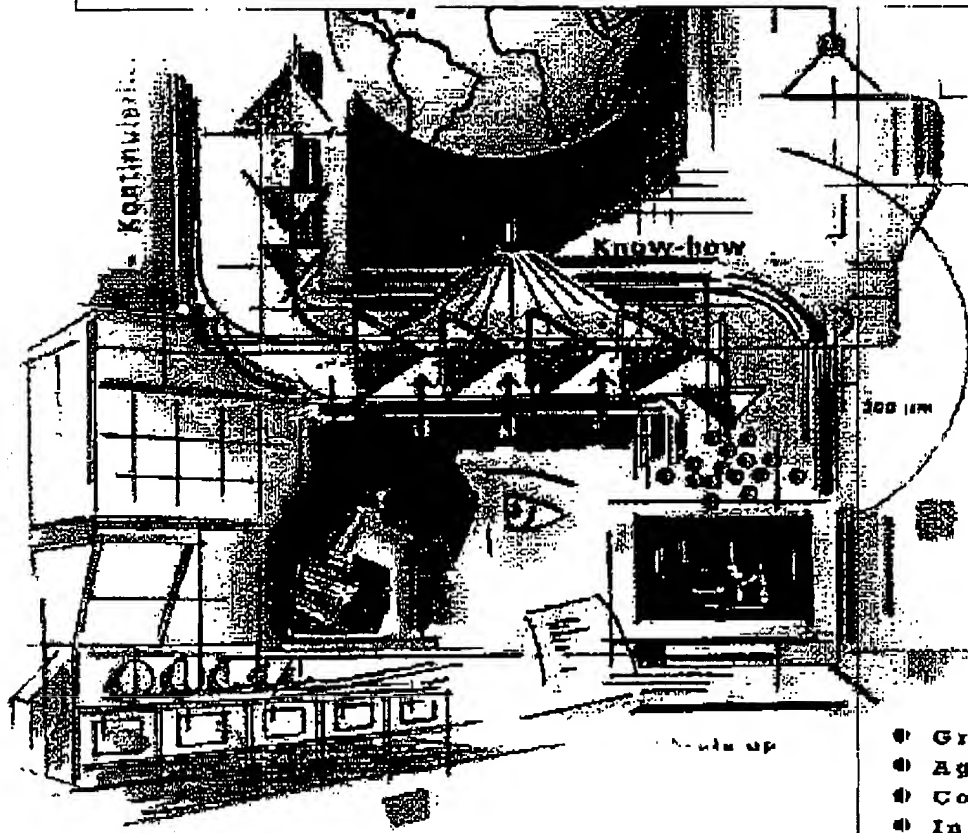
Airflow in Batch Fluid-Bed Processing

[Email this page](#)

<http://www.niroinc.com/html/pharma/airflowarticle.html> (7 de 7) [03/11/03 04:42:36 p.m.]

Attachment
3

Continuous Fluid Bed



- Granulation
- Agglomeration
- Coating
- Instantiation
- Pelletizing
- Drying

GF
ACT



We set the standards

Background

**Glatt.
Difficult processes
managed by
experience and
know how.**

What is now Glatt Ingenieurtechnik Weimar was founded in 1981 as innovation group "Continuous Fluid Bed Technology" within the research department of a large East German machine manufacturer. The task of the group was the introduction of the newly developed ACT technology in the industry. Already in 1983, the first production sized unit, an ACT for the granulation of potash solution was commercialized.



ACT 400, constructed in 1983

When the East German industry was privatized this group was taken over by the Glatt company and founded as Glatt Ingenieurtechnik in 1991. This was the start of a success story. The staff quadrupled within 10 years.

In 1988, Glatt developed the Glatt Fluid Bed (GF) in order to increase the flexibility of the continuous fluid bed processes. Originally used for drying and cooling of solids, today difficult agglomeration and coating processes can be accomplished with the GF technology.

The combination of 50 years experience with Glatt batch units in Binzen and 20 years continuous processing in Weimar results in a powerful know-how.

Besides equipment for the chemical industry, Glatt Ingenieurtechnik Weimar offers high quality equipment for the food industry. Designed according to GMP rules these units reach the well known quality of Glatt equipment and can be cleaned with WIP/CIP systems.

Contents

| | |
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| Glatt Continuous Fluid Bed - GF | 4 |
| Glatt Fluid Bed agitator | 6 |
| Unit for Continuous Granulation Drying - ACT | 7 |
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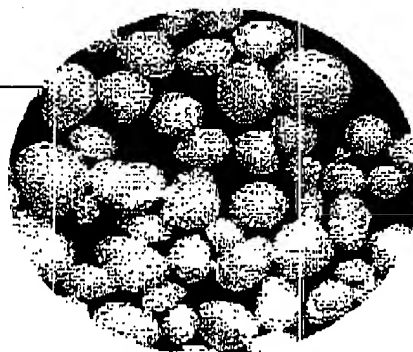


**We set
the standards**

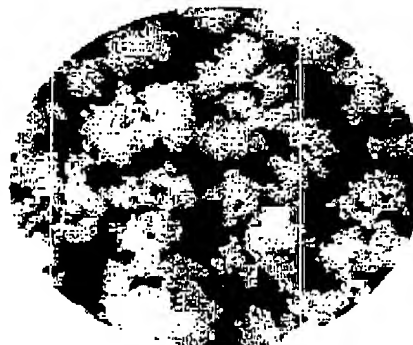
Product Advantages

Continuous fluid bed features.

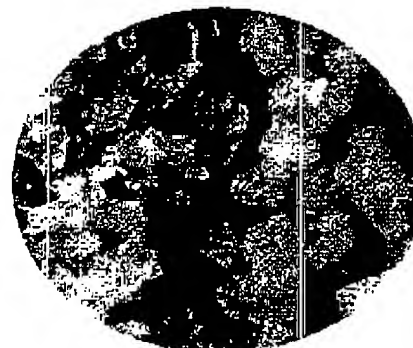
- constant product quality
- narrow grain size distribution
- dustfree and compact granules
- well disperseable and excellent soluble agglomerates
- easy to dose and to transport due to good free flowing properties
- constant filling weight and volume for packaging and pressing due to constant bulk density
- good storage properties due to a clear reduction of hygroscopicity
- no segregation of the components of a mixture



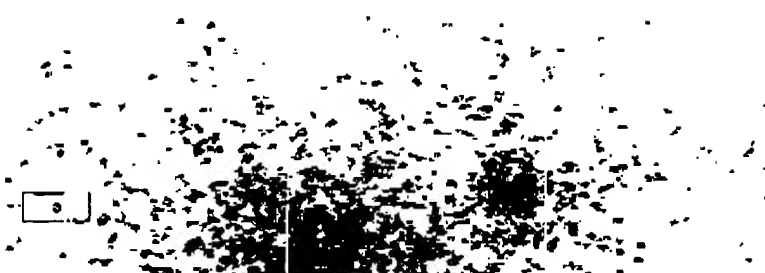
granules



agglomerates



coated crystals



Glatt Continuous Fluid Bed - GF

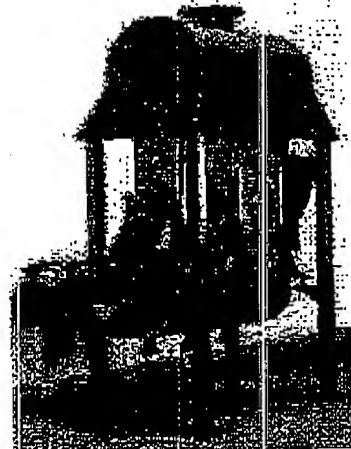
**Agglomeration.
Granulation.
Coating.
One unit for all
processes.**

Besides simple drying and cooling processes fluid bed equipment is used to build particles from powder - agglomeration - or from liquids - granulation - and to coat particles - coating.

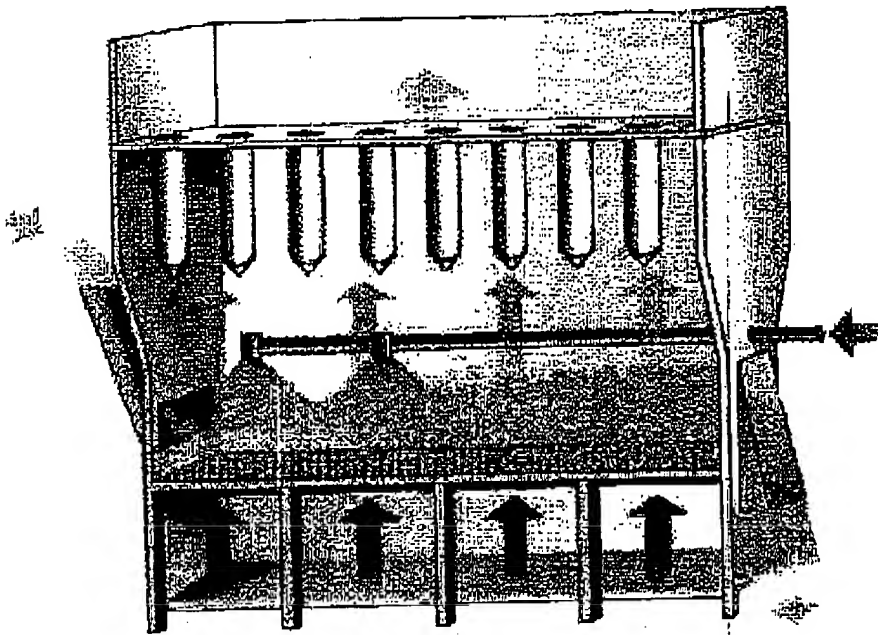
A fluid bed is formed when an upward flow of process air lifts small solid particles. As a result the small particles move rapidly within the fluid bed and ensure a very efficient heat and material exchange between the bed and the fluidizing air. The temperature in the fluid bed is constant across the whole height of the bed.

This ensures a gentle drying of temperature-sensitive products.

The continuous Glatt fluid bed can accomplish all these processes. Since the inlet air plenum is divided into multiple chambers it is possible to introduce air with different velocities and different temperatures into the processing chamber. By this means and by correct placement of the nozzles in the fluid bed, it is possible to set completely different conditions in different sections of the processing chamber.

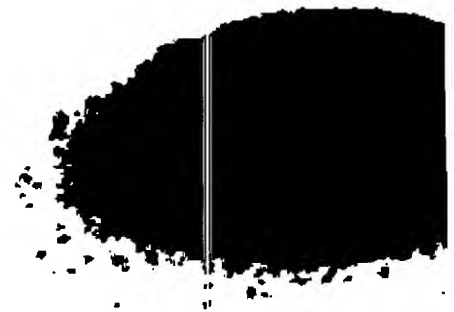


GFR 25, Glatt Fluid Bed Cooler



principle of the continuous Glatt fluid bed process

In the process shown in the principle picture, agglomerates are formed from powder above the first two inlet-air chambers. The agglomerates are dried above the third inlet-air chamber and are cooled above the fourth before they are discharged as finished product.



Flexible Construction - GF

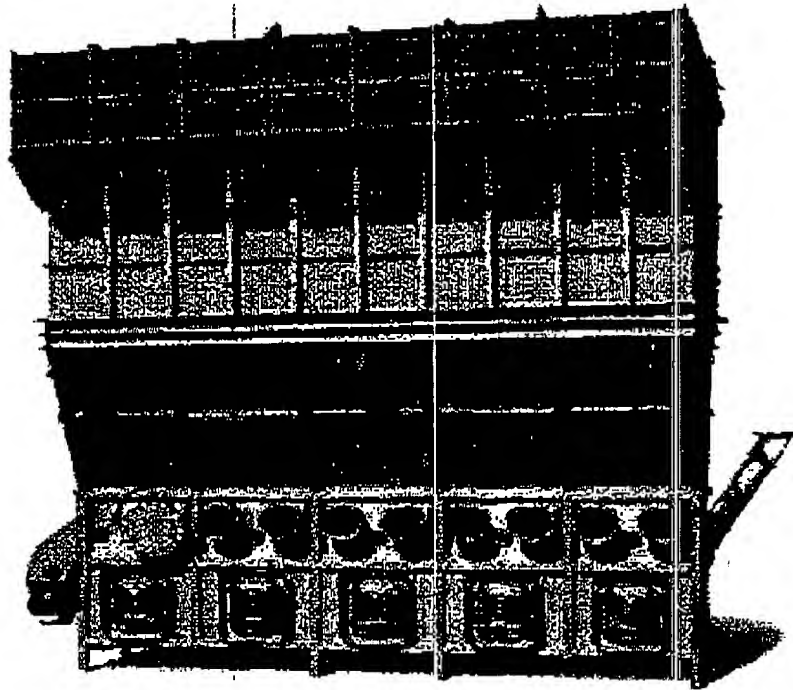
**Flexible
processes and
flexible design.**

The GF offers significant process and construction flexibility.

The standard unit consists of structural components - processing chamber, internal filter, feeding device, discharge device and spraying system. These components can be changed independently to meet the demands of the process.

If necessary the internal filter is replaced by a lid and installed externally.

The design of the spraying system allows a change of the installation of the nozzles even after the commissioning of the plant. Hence the unit can be easily adjusted to new process demands and product properties.



CFC 800, chemical plant design

Depending on the quality requirements of the end product Guld offers two versions of the GF:

- **Standard chemical plant design**
For plants with only one product or plants where product change is possible without special hygienic requirements.

Simple construction.
For high inlet air temperatures and large throughputs.

- **Standard food plant design**
For plants with high requirements on cleanliness, demand for frequent product changes.

High surface quality of product wetted parts to meet hygienic demands.

Low inlet air temperatures for temperature sensitive products.



Internal filter, CFC 80, food plant design

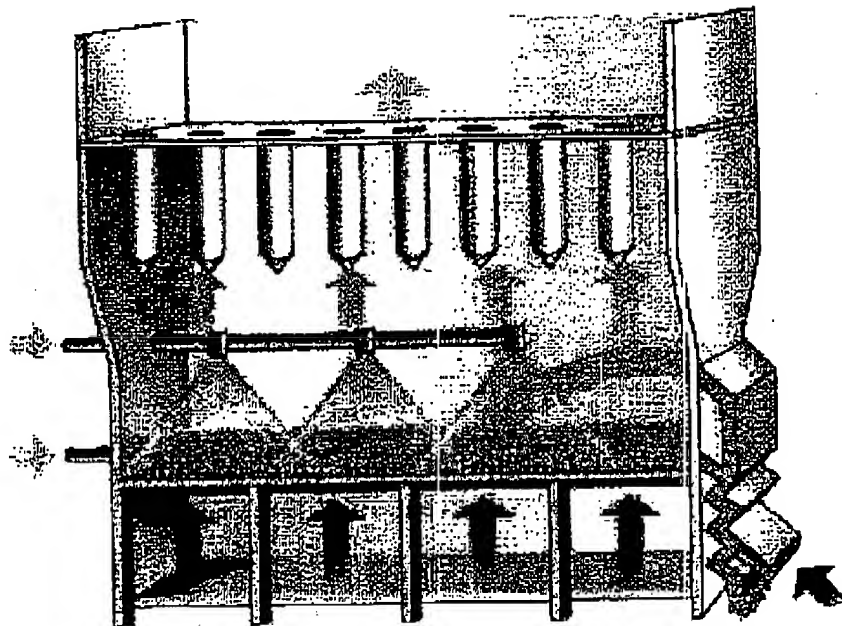


Glatt Fluid Bed Pelletizer - GFP

**A round
result -
spherical
pellets.**

For the production of very even and spherical granules, also called pellets, Glatt uses a special designed Glatt Fluid Bed - the GFP. Processed product is continuously directed into the Zig-Zag sifter where it is separated into two fractions. Only pellets of the desired grain size are discharged as product. All other pellets are blown back into the processing chamber and undergo more layering processing.

The Zig-Zag shape of the sifter ensures that no undersized pellets leave the GFP in the stream of product-sized pellets. By adjusting the flow rate of the classifying air the size of the pellets can be adjusted. Pellets as small as 200 μm can be produced. The difference from the mean pellet size may be as small as 50 μm .



principle of the continuous Glatt fluid bed pelletizer

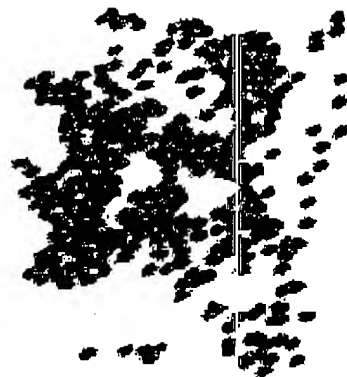


Zig-Zag sifter



SEM-picture, pellets

200 μm



Unit for Continuous Granulation Drying - AGT

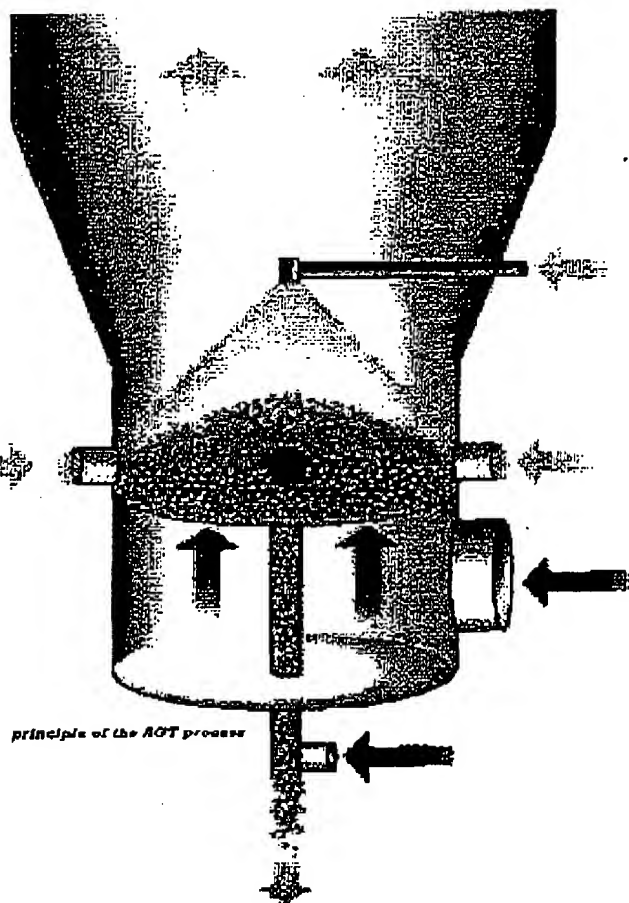
The right mixture within the AGT.

The AGT has a round bottom screen. The entire fluid bed is always ideally mixed.

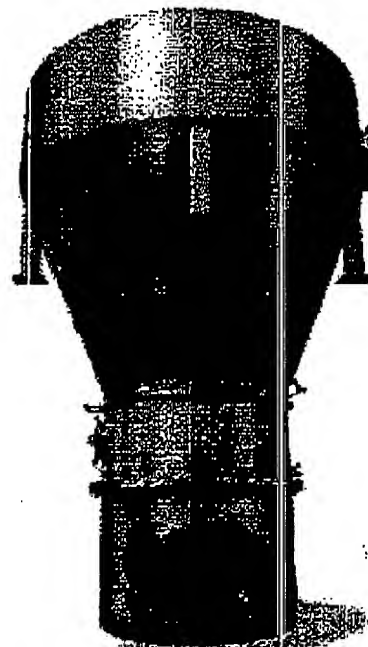
The product is discharged by means of a centrally arranged discharge pipe. The grain size of the product is determined by the velocity of the discharge air.

In most AGT processes a liquid raw material is dried while building up particle size. It is also possible to add continuously solid raw material. The fluid bed guarantees that all raw materials are mixed homogeneously in the final product.

The exhaust air is cleaned externally. All dust is recycled into the processing chamber where it is needed as seed material for the granulation process.



principle of the AGT process



AGT 2200



processing chamber, AGT 100

Explosion Protection

Securing a safe solution.

Mixtures of dust and air do frequently provide an explosion risk. Glast fluid bed equipment can therefore be equipped with explosion protection measures.

Continuous units usually offer explosion suppression systems. The pressure inside the unit is constantly monitored.



A developing explosion will cause a very fast pressure rise inside the processing chamber. If such a sharp pressure rise is monitored, pressurized vessels with extinguishing powder are emptied into the processing chamber.

A developing explosion is by this means stopped in a matter of milliseconds. The fluid bed equipment needs to withstand only a pressure of less than 1 bar.

For equipment in the food industry the explosion protection system can also be equipped with hygienic flanges and food compatible powder.

Alternatively, Glast equipment can be equipped with explosion venting devices.



ACT 400 with explosion protection system



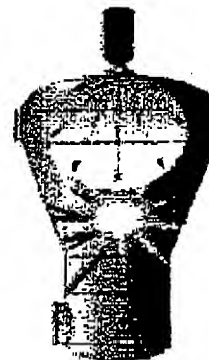
1. Ignition

time: 0 ms



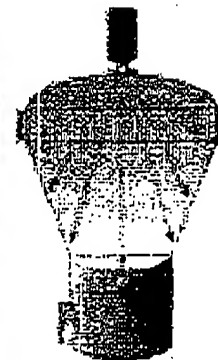
2. sensors sense the pressure rise

time: 20 ms



3. extinguishing powder is discharged

time: 30 ms



4. the extinguishing powder extinguishes the explosion flame

time: 30 ms



Cleaning Systems

**As clean
as you like.**

Simple cleaning is a cornerstone in the design of all Glatt equipment. Easy access to all parts of the machinery, correctly placed revision doors and cleaning water drains as well as the installation of cleaning nozzles are part of this philosophy.

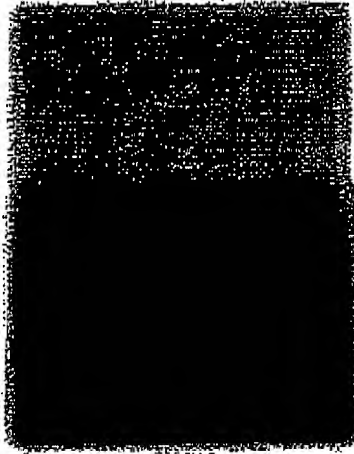
Units for the food industry which have to be cleaned frequently for hygienic reasons are offered with comprehensive wash in place systems. Glatt has many years of experience with the design of WIP and CIP systems.

Many design criteria need to be addressed to ensure an automatic cleaning e.g.:

- high surface quality of all product contact parts
- easily detachable spray nozzles
- special flanges without gaps
- special sensors for process parameters
- correct arrangement of cleaning nozzles
- optimal drainage of cleaning water



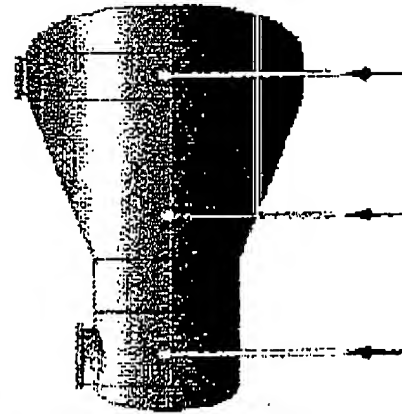
Flush mounted, hydraulically extending washing nozzle



WIP skid

In every unit the cleanability of the filter is decisive for the cleaning system. Glatt offers three designs to meet different demands:

- two sets of filters which are exchanged and cleaned outside
- sintered ceramic filters which can be cleaned in place but need to be checked afterwards



principle of automatic cleaning



*Glatt metal cartridge filter
SC SuperClean®*

- Glatt metal cartridge filters SC SuperClean® which can be cleaned in place and guarantee absolute cleanliness

Process Development

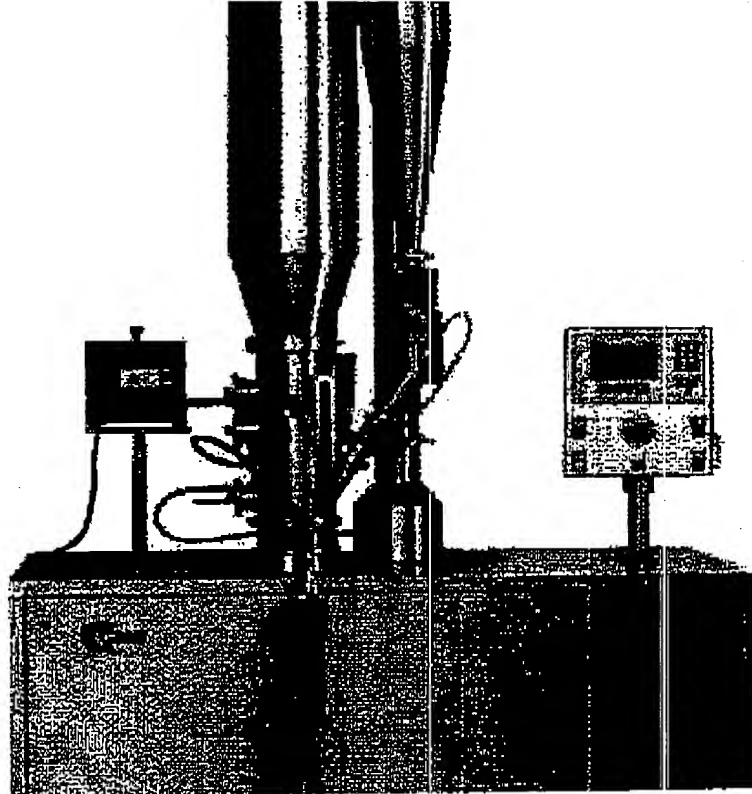
**Long
experience -
Short
process.**

Process development is performed in Glatt laboratories where the experience of the customer with his product is combined with the process know how of the Glatt engineers.

First, feasibility trials are carried out in small batch and continuous units with a throughput of 1-2 kg/h.

Further process development is done on pilot scale units with up to 80 kg/h throughput. Based on the determined parameters our engineers scale up and size the production equipment for the desired throughput. Fifty years experience and the process simulation program ChemCAD are the powerful tools used when scaling up.

After a thorough process development experience Glatt guarantees certain product and process parameters.



GCT 150

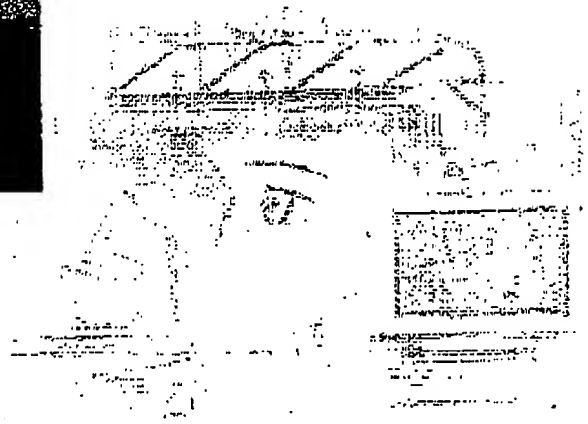


small units for feasibility trials



analytical laboratory

The laboratory units are mobile. Customers can rent the units for product development in their own laboratory.



Engineering

**Service
as requested,
engineered
success provided.**

Besides the core unit GF or AGT, Glatt delivers all peripheral equipment necessary for the operation of the process, like fans, pumps and transport systems.

Further equipment needed for an optimal handling of the raw materials and the product can also be commissioned, like mixers, dosing devices and packaging machines.

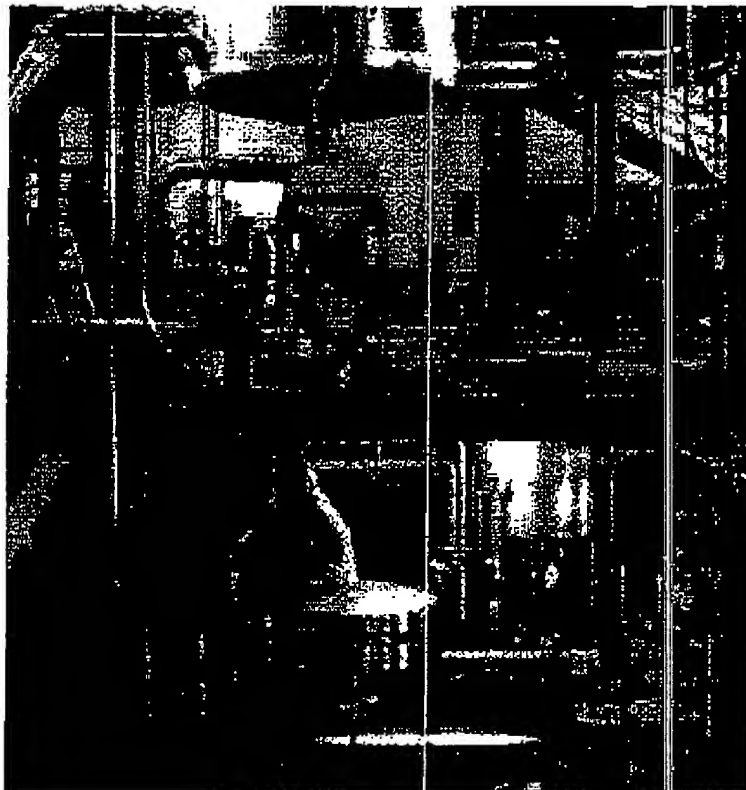
Modern software tools, like CAD and FEM are used to provide an excellent service to the customer.

Glatt also works as a prime contractor, designing and commissioning entire plants, including the building.

Control system as desired.
Standard Glatt equipment is controlled with a PLC by SIEMENS (Europe) or by ALLAN BRADLEY (USA).
On request different control systems can be used. Several other systems have successfully been installed, such as Mitsubishi and Freelance.
The process visualization is generally done using the desired program.



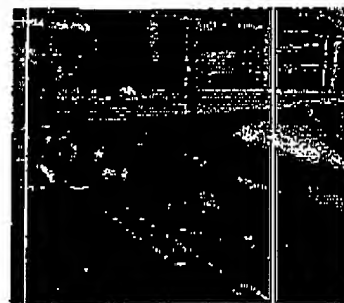
plant optimization by simulation



realization of an entire production plant

Installation, start up and training.
Glatt offers expertise in the installation and commissioning of the plant.
Glatt engineers start the plant up and train the customer staff.

Good technical support and a prompt spare part service provide long term customer satisfaction.



production plant, AGT 1800

Technical Data

| Glatt Fluid Bed Unit-GT | | | | | | |
|----------------------------|--------|----------------------------|-----------|-----------|-----------|-----------|
| bottom screen area | m² | 0.2 | 0.8 | 1.25 | 2.5 | 5.0 |
| raw materials | Liquid | solution, suspension, melt | | | | |
| fluid plant design | | | | | | |
| water evaporation 1) | kg/h | 15 | 40 | 100 | 198 | 386 |
| width B ₁ | mm | 200 | 380 | 500 | 760 | 1000 |
| height H | mm | 2900 | 2800 | 5800 | 5900 | 6100 |
| inlet air chambers | | 3 | 3 | 4 | 4 | 5 |
| heating capacity 1) | kW | 23 | 57 | 138 | 278 | 554 |
| inlet air temperature 1) | °C | 175 | | | | |
| length L | mm | 1500 | 2000 | 2300 | 3400 | 5700 |
| width B ₂ | mm | 1300 | 1300 | 2000 | 3000 | 3200 |
| filter system | | bag filter | | | | |
| electrical power supply 2) | kW | 8 ... 13 | 16 ... 20 | 20 ... 23 | 31 ... 39 | 47 ... 78 |

remarks:

¹⁾ value for standard design

²⁾ estimated value for common air flow rates

³⁾ installed power supply for fans, pumps and rotary valves

⁴⁾ for heating of fresh air from -15°C to the inlet air temperature

| Glatt Unit for Granulation Drying-AGT | | | | | | |
|---------------------------------------------|----------------|----------------------------|----------|-----------|-----------|-----------|
| | Type | AGT 100 | AGT 250 | AGT 500 | AGT 750 | AGT 1000 |
| bottom screen area | m ² | 0.1 | 0.5 | 1.1 | 1.8 | 3.8 |
| raw materials | liquid | solution, suspension, melt | | | | |
| chemical plant design | | | | | | |
| water evaporation ¹⁾ | kg/h | 60 | 240 | 540 | 840 | 1800 |
| diameter, processing chamber D _s | mm | 800 | 1500 | 2200 | 2700 | 3800 |
| electrical power supply ²⁾ | kW | 8 ... 13 | 8 ... 13 | 11 ... 18 | 18 ... 22 | 25 ... 39 |

remarks:

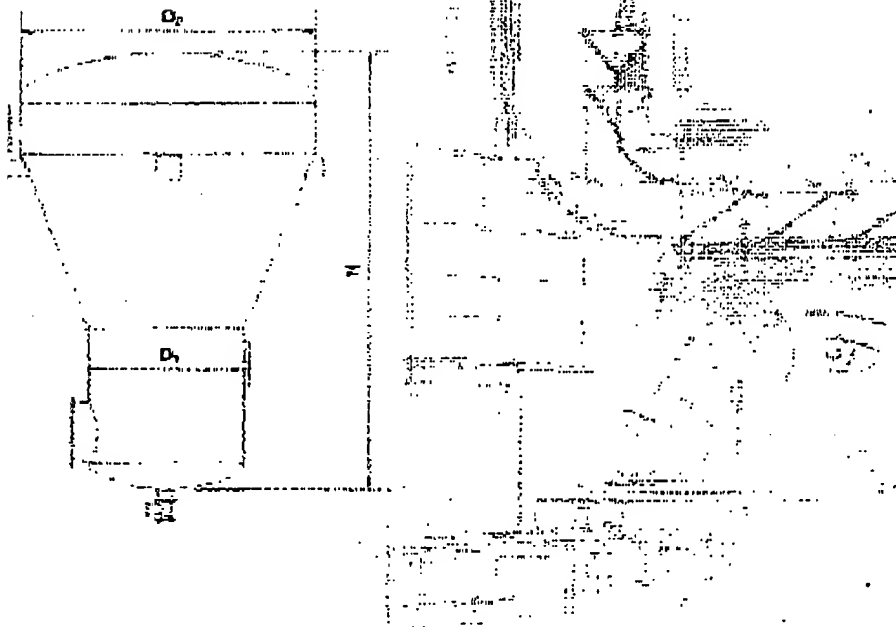
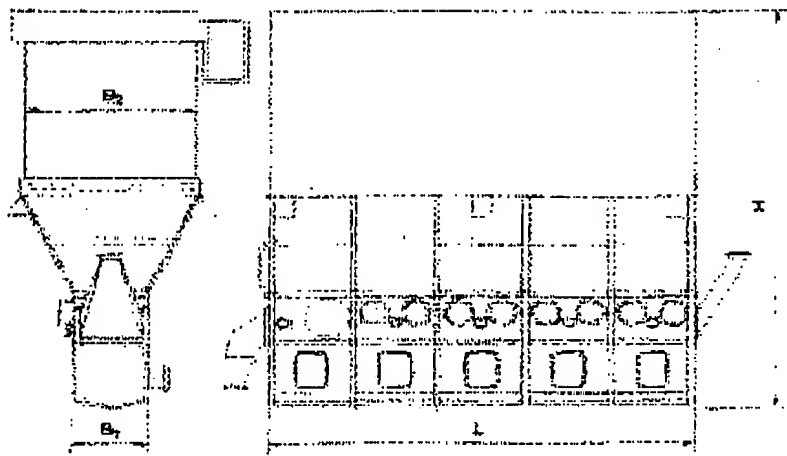
¹⁾ value for standard design

²⁾ estimated value for common air flow rates

³⁾ installed power supply for fans, pumps and rotary valves

⁴⁾ for heating of fresh air from -15°C to the inlet air temperature

| | |
|------------|-------------|
| 7.5 | 10 |
| 590 | 770 |
| 1500 | 1500 |
| 8100 | 8100 |
| 6 | 6 |
| 630 | 1104 |
| 6800 | 7900 |
| 3800 | 3800 |
| 77 ... 113 | 120 ... 140 |



13

Glatt Service Program

**Equipment,
engineering and
services, out of
one source.**

**Engineering
and Service**

Product Development
development and optimization
of your products in Glatt
laboratories.

Glatt equipment

Batch Fluid Bed Equipment
as dryer, with spraying system
as granulator, with Wurster
insert for coating, with rotor
insert for powder layering.

Fan Coater GC
for film coating of tablets.

Vertical Granulator VG
for wet granulation of powders.

Pelletizer
for spherulization of extrudates.

Product Handling
hoppers, container, container
mixer, sieves and pneumatic
transport systems.

Vacuum Dryer
with different agitation systems
for drying of vacuum products.

Engineering
Glatt engineers and commissions
production lines up to turn key
plants.

Qualification and Validation
Glatt supplies all documents
needed for a comprehensive
qualification and validation of the
equipment.

Toll Manufacturing
Glatt also manufactures product
with Glatt equipment. So you
can considerably shorten your
time to market.

Training
Glatt offers courses on specific
subjects or organizes individual
training programs.

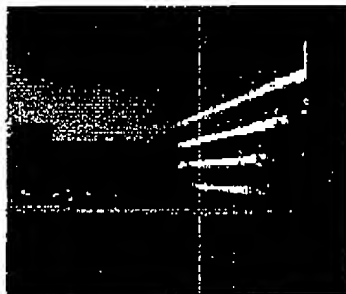


technology center, Glatt

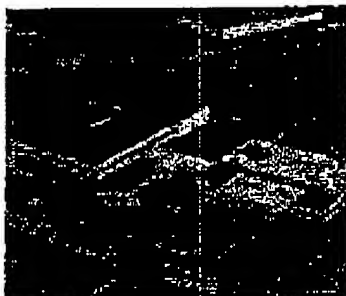
Addresses



**World wide
service to the
customer.**



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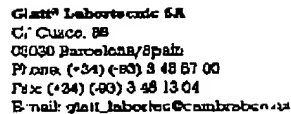
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20 Spear Road
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Phone: (+1) (801) 825 67 00
Fax: (+1) (801) 825 03 89
E-mail: info@glattair.com



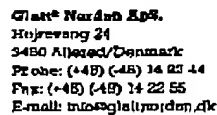
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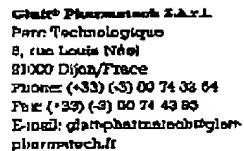
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Swannington Rd. Colleyes Lane Ind. Est.
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Fax: (+44) (0)1455 28 68 10
E-mail: info@glaxo-protech.co.uk



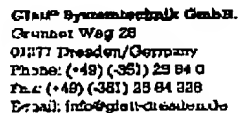
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